THE PHENOMENA OF ANAPHYLAXIS AND ALLERGY AND THEIR RELATIONSHIP TO IMMUNITY

By FRASER B. GURD, B.A., M.D.

Montreal

THE discovery of the phenomena of anaphylaxis and allergy in 1906 has had such a vital influence upon the science of immunology that a proper conception of their nature is essential, if we are to be able to follow the recent and future advances in the knowledge of immunity processes.

In this short paper I shall attempt briefly to review the established characteristics of the two phenomena and indicate their relationship to one another and to immunity processes in general. In doing so I will adopt a frankly didactic rather than an argumentative or discursive attitude, in order that as clear a conception of the importance of these reactions may be obtained, as possible.

Should it prove desirable, the arguments supporting and opposing the views outlined can be considered in the discussion which is to follow.

By the term anaphylaxis (Richet) is designated the constitutional phenomena accompanying protein hypersensitiveness, while by allergy (von Pirquet) is meant the local or focal altered reactions which take place upon reintroduction of protein materials into sensitive individuals.

The experiments which are detailed in the following paragraphs exemplify certain of the more striking characteristics of the anaphylactic reaction.

If a series of half-grown guinea pigs each receive a dose of 0·2 cubic centimetres of sheep serum and subsequently be subjected to the following treatments certain striking and interesting results may be demonstrated.

G.P.A. may be given within five days of the first injection from 0·2 to 2·0 cubic centimetres of sheep serum without manifesting untoward symptoms.

Contributed to the symposium on Immunity, Montreal Medico-Chirurgical Society, December 4th, 1914.

G.P.B. fourteen days after the preliminary injection receives an intravenous injection of 0·5 cubic centimetres of sheep serum. Within a period of one or two minutes the animal will show evidences of grave irritation and will die within from three to eight minutes.

These manifestations consist of evidences of pruritis—scratching and sneezing; dyspnœa,—cough, cyanosis, slowed and forced expiratory effort with gradual cessation of respiration; nervous irritation,—convulsions and coma. Upon examination may be found drop in temperature, drop in blood pressure and leucopenia.

Immediate autopsy reveals the fact that the heart is still beating, the lungs are distended and present numerous hæmorrhagic areas, there may be marked splanchnic congestion.

The above may be looked upon as the typical anaphylactic experiment in the guinea pig and is known as anaphylactic shock.

G.P.C. is injected upon the same day as G.P.B. with an intraperitoneal dose of 0·2 cubic centimetres of sheep serum. There will be no immediate onset of symptoms, but within a period of one half to one hour the animal will be found to be suffering from malaise; the hair will stand on end and the pig will huddle itself in a corner and may shiver and be obviously unhappy.

The temperature will at first drop slightly and then show an elevation above the normal; a transient leucopenia occurs followed by leucocytosis. A scant purulent exudate may be recovered from the peritoneal cavity. The animal will recover within 24 hours.

We have thus discovered that if an animal which is susceptible to anaphylactic shock be given a *small* dose of protein a simple febrile reaction occurs.

Upon the following day G.P.C. is injected in a manner and with an amount of serum similar to G.P.B. No evidences of intoxication are found. This and other experiments prove that this animal has been desensitized; while in this state the animal is said to be refractory.

G.P.D. receives upon the fourth day after the original injection of 0·2 cubic centimetres an intraperitoneal injection of 2·0 cubic centimetres of sheep serum, and thereafter a like amount on three or more successive occasions at intervals of five or six days.

After a lapse of from twelve to sixty days after the last injection a dose similar to that introduced into G.P.B. is injected intravenously. No reaction takes place. If, however, a large dose, 3·0 cubic centimetres of sheep serum, be injected, typical anaphylactic shock with death will supervene.

This experiment demonstrates that an animal which receives repeated doses of protein remains hypersensitive to this protein, but that large toxic injections must be employed in order to bring about anaphylactic shock.

Another pig, G.P.C., fourteen days after the sensitizing injection of 0·2 cubic centimetres of sheep serum, is bled to death and its serum recovered. The serum thus obtained is injected into a normal pig with the result that the latter becomes highly hypersensitive. In order that such a transference of the anaphylactic state may be brought about, it is necessary to inject from two thirds to the total amount of serum recovered.

Similarly, if the serum of an animal treated in the manner of G.P.D. be injected into a normal pig, the latter becomes passively hypersensitive. It is found, moreover, that but a very small amount of serum, e.g., 0·1 cubic centimetre, is necessary.

The paradoxical phenomena are thus noted, that the serum of an animal, whose hypersensitiveness is easily demonstrated, contains but a small number of units of the anaphylactic body, whereas the serum of an animal in whom hypersensitiveness is proven only by the employment of large toxic doses of protein, contains a very large number, 100 to 200, or more, of units.

Obviously the animal D is not desensitized as was C, but has developed a state which may be described as immunity to the protein. At the same time it is noticed that *the more highly immune an animal may be, the greater is its potential hypersensitiveness.*

How, then, can the relationship of these two conditions of hypersensitiveness and immunity be explained? First, let us note that it is possible to transfer passive immunity to a normal animal by the employment of large doses, 2·0 cubic centimeters, of the serum from the repeatedly injected animal and also to confer immunity upon an actively sensitized animal such as G.P.B.

The sequence of changes which occurs in the animal's tissues is believed by the author to be somewhat as follows. Complex proteins, such as serum albumin, are not toxic to the tissue cells; they are, however, foreign and useless. The body, therefore, produces an antibody which acts upon the protein in such a way that a toxic substance (split-product) is formed. The animal whose tissues contain this antibody is then hypersensitive to such a protein. Reinjection of the protein in sublethal doses stimulates not only an increased production of the anaphylactic antibody but also a second order of antibodies which are able to neutralize or detoxicate the toxic product arising from the action of the first or anaphylactic antibody upon the protein.

The work of Vaughan, Abderhalden and others upon parenteral digestion makes it appear as if many, if not all, the phenomena of immunity may yet be explained in this way. If we attempt to bring the reactions of anaphylaxis into line in this fashion we have but to consider the anaphylactic body as being in the nature of a peptic ferment, and the second order, or immunizing body, as an ereptic ferment.

The peptic ferment reduces the protein to peptones and proteoses which are toxic, while the ereptic ferment causes cleavage of these substances, with the production of harmless or even utilizable peptids and amino-acids.

Allergy

When a normal individual is inoculated with smallpox virus a period of three days intervenes before an inflammatory reaction occurs. Once commenced this progresses for another week until an acute pustule is formed. If, however, the individual has been previously vaccinated, within a period of two years, the tissues react in a different fashion, hence, allos-altered, ergos-reaction, allergy.

In this altered reaction the hyperæmic stage is reached after the lapse of but a few hours, nor does it progress to a stage of pustulation, but is of short duration and does not go beyond the stage of hyperæmia with slight œdema.

The essential feature of this reaction is in the shortening of the incubation period. If the cells and vessels react soon after the introduction of the virus a less pronounced reaction will suffice to destroy the invader, since but little proliferation of the latter will have had time to take place.

This curtailing, or elimination, of the incubation period may be explained as follows: Morphologic tissue reactions—that is, vascular dilatation and cellular activity—occur only when the tissues are irritated. This may be demonstrated by the simple experiment of burying in the tissues two pieces of catgut one of which has been dipped in turpentine. At the site of the plain gut no reaction is noted, whereas an abscess forms about the turpentine-soaked gut. The vaccinia virus is essentially nontoxic and hence does not irritate the tissues. No reaction, therefore, occurs until such time as there has been produced in the tissues a body capable of so acting upon the virus that a toxic product is liberated. So soon as this toxic substance is developed the morphologic reaction commences, the de-

gree of reaction depending upon the number of units of virus which have been acted upon.

If it be borne in mind that of the two offensive methods at the disposal of the body whereby infection is overcome, cellular phagocytosis is much the more potent, granted that it may be induced to take place, the importance of the hypersensitive stage in stimulating the allergic reaction is manifest. *Under normal conditions protection of the individual against infection depends upon hypersensitiveness to the bacterial protein.*

The employment of bacterio-proteins or vaccines in prophylaxis or cure of disease is to be dealt with in other papers. Permit me, however, to indicate the problems which confront us in our efforts in that direction based upon our knowledge of anaphylaxis and allergy.

By means of the injection of bacterio-proteins or vaccines various results may be obtained, depending upon (1) the state of the individual injected; (2) the dose of bacterio-protein injected and (3) the interval allowed between injections. Thus any one of the following four alterations in the hypersensitiveness may occur.

1. Hypersensitiveness may be induced if such be absent, or increased if already present.

2. Hypersensitive individuals may be desensitized.

3. Both hypersensitiveness and immunity may be developed by means of repeated injections.

4. In chronically infected individuals where immunity suffices to mask their hypersensitiveness the immunizing bodies may be depressed so that their hypersensitiveness becomes more apparent and allergic reactions are stimulated.

5. Both sensitizing and immunizing bodies may be depressed to such a degree that all cellular and vascular reactions cease.

It is thus seen that in the employment of vaccines or bacteroproteins for clinical purposes we are, to say the least, dealing with a two-edged sword. In order, therefore, that favourable results may follow such inoculation procedures it is necessary that the physician know, relatively at least, the degree of sensitiveness of the individual to be treated and have a clear conception of the alterations, in the tissue and serum reactions, which he wishes to stimulate.